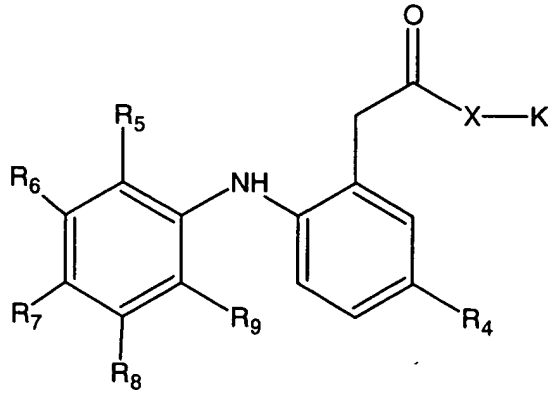
CLAIMS

What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is:



(I)

wherein:

R_4 is methyl or ethyl;

R_5 is chloro or fluoro;

R_6 is hydrogen or fluoro;

R_7 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

R_8 is hydrogen or fluoro;

R_9 is chloro, fluoro, triflurormethyl or methyl;

X is an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$;

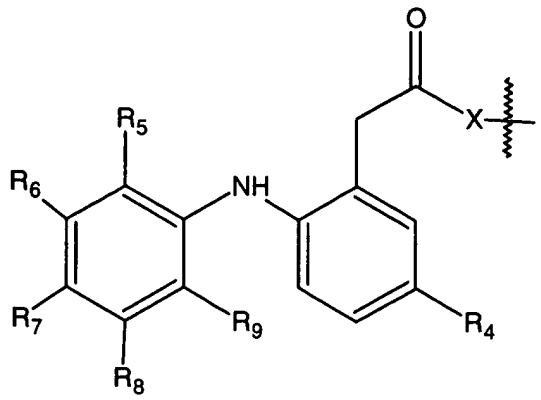
K is:

a) $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-T-Q$; or

b) $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-R_3$ and

with the proviso that at least one R_e is selected as -T-Q , or $-(C(R_g)(R_h))_k-T-Q$ when K is (b); and with the further proviso that "X-K" in the compounds of Formula (I), does not include nitroxyl lower alkyl esters;

R_3 is:



Q is –NO or -NO_2;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently -C(O)-, -C(S)-, -T-, -$(C(R_e)(R_f))_h$-, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, or -$(CH_2CH_2O)_q$-;

E at each occurrence is independently -T-, an alkyl group, an aryl group, -$(C(R_e)(R_f))_h$-, a heterocyclic ring, an arylheterocyclic ring, or -$(CH_2CH_2O)_q$-;

h is an integer form 1 to 10;

q is an integer from 1 to 5;

R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, an alkylcycloalkyl, an alkylheterocyclic ring, a cycloalkylalkyl, a cycloalkylthio, a cycloalkenyl, an heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, arylsulphonyloxy, a sulfonic ester, a urea, a phosphoryl, a nitro, W_h, -T-Q , or -$(C(R_g)(R_h))_k$-T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group, an aryl group, an oxime, a hydrazone or a bridged cycloalkyl group;

R_g and R_h at each occurrence are independently R_e;

k is an integer from 1 to 3;

T at each occurrence is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$;

o is an integer from 0 to 2;

R_a is a lone pair of electrons, a hydrogen or an alkyl group;

R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyl, arylsulphonyloxy, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2-C(T-Q)(R_e)(R_f)$, a bond to an adjacent atom creating a double bond to that atom, $-(N_2O_2-)^-\bullet M^+$, wherein M^+ is an organic or inorganic cation;

with the proviso that the nitrosated and/or nitrosylated compounds of Formula (I) must contain at least one –NO group or at least one $-NO_2$ group, and wherein the at least one –NO group or the at least one $-NO_2$ group is linked to the compounds of Formula (I) through an oxygen atom, a nitrogen atom or a sulfur atom.

2. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

3. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

4. A method for treating a gastrointestinal disorder, or improving the gastrointestinal properties of a COX-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

5. The method of claim 4, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

6. A method for facilitating wound healing in a patient in need thereof comprising

administering to the patient a therapeutically effective amount of the composition of claim 2.

7. The method of claim 6, wherein the wound is an ulcer.

8. A method for treating or reversing renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

9. A method for treating a disorder resulting from elevated levels of COX-2 in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

10. The method of claim 9, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin-related condition, neoplasia, inflammatory processes in diseases, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, preservation of organs and tissues, inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or inhibition of platelet aggregation.

11. The method of claim 10, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

12. The method of claim 10, wherein the central nervous system disorder is cortical dementias, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, central nervous system damage resulting from stroke, ischemia or trauma.

13. A method for inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

14. The composition of claim 2, further comprising at least one therapeutic agent.

15. The composition of claim 14, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a HMG CoA inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

16. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

17. A method for treating a gastrointestinal disorder, or improving the gastrointestinal properties of a COX-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

18. The method of claim 17, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

19. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 84.

20. The method of claim 19, wherein the wound is an ulcer.

21. A method for treating or reversing renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

22. A method for treating a disorder resulting from elevated levels of COX-2 in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

23. The method of claim 22, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor,

tendinitis, bursitis, skin-related condition, neoplasia, inflammatory processes in diseases, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, preservation of organs and tissues, inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or inhibition of platelet aggregation.

24. The method of claim 23, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

25. The method of claim 23, wherein the central nervous system disorder is cortical dementias, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, central nervous system damage resulting from stroke, ischemia or trauma.

26. A method for inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

27. A composition comprising at least one compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

28. The composition of claim 27 further comprising a pharmaceutically acceptable carrier.

29. The composition of claim 27, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

30. The composition of claim 29, wherein the S-nitrosothiol is S-nitroso-N-

acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, or S-nitroso-cysteinyl-glycine.

31. The composition of claim 29, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q-, or $-(C(R_g)(R_h))_k$-T-Q or R_e and R_f taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2\text{-}C(T\text{-}Q)(R_g)(R_h)$, or $-(N_2O_2\text{-})^{\cdot}\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2\text{-}C(T\text{-}Q)(R_g)(R_h)$ or $-(N_2O_2\text{-})\bullet M^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and R_g and R_h at each occurrence are independently R_e.

32. The composition of claim 27, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-

derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine, nitrosylated L-homoarginine), citrulline, ornithine, glutamine, lysine, an arginase inhibitor or a nitric oxide mediator.

33. The composition of claim 27, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O- or ON-N- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N- or O_2N-S- or group;

(iii) a N-oxo-N-nitrosoamine having the formula: $R^{1''}R^{2''}N$-N(O-M^+)-NO, wherein $R^{1''}$ and $R^{2''}$ are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

34. The composition of claim 33, wherein the compound comprising at least one ON-O- or ON-N- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, an ON-O-heterocyclic compound or an ON-N-heterocyclic compound.

35. The composition of claim 33, wherein compound comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, , a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound or an O_2N-S-heterocyclic

compound.

36. The composition of claim 37, further comprising at least one therapeutic agent.

37. The composition of claim 36, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a HMG CoA inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

38. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 27 or 36.

39. A method for treating a gastrointestinal disorder, or improving the gastrointestinal properties of a COX-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 27 or 36.

40. The method of claim 39, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

41. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 27 or 36.

42. The method of claim 41, wherein the wound is an ulcer.

43. A method for treating or reversing renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 27 or 36.

44. A method for treating a disorder resulting from elevated levels of COX-2 in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 27 or 36.

45. The method of claim 44, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin-related condition, neoplasia, inflammatory processes in diseases, ophthalmic disorder, pulmonary inflammation, system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, preservation of organs and tissues, inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or inhibition of platelet aggregation.

46. The method of claim 45, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

47. The method of claim 45, wherein the central nervous system disorder is cortical dementias, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, central nervous system damage resulting from stroke, ischemia or trauma.

48. A method for inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claims 27 or 36.

49 A kit comprising at least one compound of claim 1 or a pharmaceutically acceptable salt thereof.

50. The kit of claim 49, further comprising at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase or at least one therapeutic agent.

51. The kit of claim 50, wherein the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived

relaxing factor, or is a substrate for nitric oxide synthase or the at least one therapeutic agent are in the form of separate components in the kit or are in the form of a composition in the kit.

52. A kit comprising the composition of claim 14, 27 or 36.

53. The compound of claim 1, wherein the compound of claim 1 is a nitrosated 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetate, a nitrosylated 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetate, a nitrosated and nitrosylated 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetate or a pharmaceutically acceptable salt thereof..

54. A compound selected from the group consisting of 2-(2-(nitroxy)ethylthio)ethyl 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetate, 2-(2-(nitroxy)ethoxy)ethyl 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetate, 3-((nitroxy)methylphenyl) 2(2-((2-chloro-6- fluorophenyl) amino)5- methylphenyl)acetate, 2,3-bis(nitroxy)propyl 2(2-((2-chloro-6-fluorophenyl)amino)5-methylphenyl)acetate, 6-(nitroxy)-4,8-dioxabicyclo(3.3.0)oct-2-yl 2-(2-((2-chloro-6- fluorophenyl)amino)5-methylphenyl)acetate, 2-((2-(nitroxy)ethyl)sulfonyl) ethyl 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetate, 2-(4-(2-nitrooxyl)ethyl) piperazinyl)-2-oxoethyl 2-(2-((2-chloro-6- fluorophenyl)amino)5-methylphenyl)acetate, 2,3-bis(nitroxy)-4-(2-(2-((2-chloro-6- fluorophenyl)amino)5-methylphenyl)acetyloxy)butyl 2-(2-((2-chloro-6- fluorophenyl)amino)5-methylphenyl)acetate, 2-(2-(hydroxyethylthio)ethyl 2(2-((2-chloro- 6-fluorophenyl) amino)5- methylphenyl)acetate, 2-(2-(hydroxyethoxy)ethyl 2(2-((2-chloro- 6-fluorophenyl) amino)5- methylphenyl)acetate, 3-(hydroxymethylphenyl) 2(2-((2-chloro-6- fluorophenyl) amino)5-methylphenyl)acetate, 2,3-dihydroxypropyl 2(2-((2-chloro-6-fluorophenyl)amino)5-methylphenyl)acetate, 6-hydroxy-4,8-dioxabicyclo(3.3.0)oct-2-yl 2(2-((2-chloro-6-fluorophenyl)amino)5-methylphenyl)acetate, 2-((2-hydroxyethyl)sulfonyl) ethyl 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetate, 2-(4-(2-hydroxyethyl)piperazinyl)-2-oxoethyl 2-(2-((2-chloro-6- fluorophenyl)amino)5-methylphenyl)acetate, 4-(2-(2-((2-chloro-6-fluorophenyl)amino)5-methylphenyl)acetoxy)-2,3-dihydroxybutyl-2-(2-((2-chloro-6-fluorophenyl)amino)5-methylphenyl)acetyloxy)butyl acetate, or a pharmaceutically acceptable salt thereof.

55. A composition comprising at least one compound of claim 54 and a pharmaceutically acceptable carrier.

56 A kit comprising at least one compound of claim 54 or a pharmaceutically acceptable salt thereof.

57. A composition comprising at least one parent COX-2 inhibitor of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

58. The composition of claim 57 further comprising a pharmaceutically acceptable carrier.

59. The composition of claim 57, wherein the parent COX-2 inhibitor of Formula (I) is 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetic acid.

60. The composition of claim 57, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

61. The composition of claim 60, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, or S-nitroso-cysteinyl-glycine.

62. The composition of claim 60, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q-, or $-(C(R_g)(R_h))_k\text{-}T\text{-}Q$ or R_e and R_f taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl,

an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2-C(T-Q)(R_g)(R_h)$, or $-(N_2O_2-)^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2-C(T-Q)(R_g)(R_h)$ or $-(N_2O_2-)\bullet M^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and R_g and R_h at each occurrence are independently R_e.

63. The composition of claim 57, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine, nitrosylated L-homoarginine), citrulline, ornithine, glutamine, lysine, an arginase inhibitor or a nitric oxide mediator.

64. The composition of claim 57, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O- or ON-N- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N- or O_2N-S- or group;

(iii) a N-oxo-N-nitrosoamine having the formula: $R^{1''}R^{2''}N-N(O-M^+)-NO$, wherein $R^{1''}$ and $R^{2''}$ are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

65. The composition of claim 64, wherein the compound comprising at least one ON-O- or ON-N- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted,

aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, an ON-O-heterocyclic compound or an ON-N-heterocyclic compound.

66. The composition of claim 64, wherein compound comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, , a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound or an O_2N-S-heterocyclic compound.

67. The composition of claim 57, further comprising at least one therapeutic agent.

68. The composition of claim 67, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a HMG CoA inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

69. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 57 or 67.

70. A method for treating a gastrointestinal disorder, or improving the gastrointestinal properties of a COX-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 57 or 67.

71. The method of claim 70, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel

(anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

72. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 57 or 67.

73. The method of claim 72, wherein the wound is an ulcer.

74. A method for treating or reversing renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 57 or 67.

75. A method for treating a disorder resulting from elevated levels of COX-2 in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 57 or 67.

76. The method of claim 75, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin-related condition, neoplasia, inflammatory processes in diseases, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, preservation of organs and tissues, inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or inhibition of platelet aggregation.

77. The method of claim 76, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

78. The method of claim 76, wherein the central nervous system disorder is cortical dementias, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, central nervous system damage resulting from stroke,

ischemia or trauma.

79. A method for inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claims 57 or 67.

80. A kit comprising at least one parent COX-2 inhibitor and at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, or a pharmaceutically acceptable salt thereof, or at least one therapeutic agent.

81. The kit of claim 80, wherein the at least one parent COX-2 inhibitor and compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase or the at least one therapeutic agent are in the form of separate components in the kit or are in the form of a composition in the kit.